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# Trastuzumab-Related Cardiotoxicity in Early Breast Cancer: A Cohort Study

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*Disclosures of potential conflicts of interest may be found at the end of this article.*

**Key Words.** Trastuzumab • Early breast cancer • Adjuvant chemotherapy • Cardiotoxicity • Survival

**Learning Objectives**

Evaluate the frequency of trastuzumab-related serious cardiac events in clinical practice.

Assess the cumulative incidence of cardiac disorders at 1, 2, and 3 years after first administration, irrespective of drug discontinuation.

Identify predictors for the onset of cardiotoxicity.

## ABSTRACT

***Background.*** Concerns have been raised about the cardiac safety profile of trastuzumab for the adjuvant treatment of early stage breast cancer in clinical practice. We assessed trastuzumab-related cardiotoxicity and its predictors in a large cohort of Italian women.

***Methods.*** Through a record linkage between four regional health care databases, we identified the rate of severe cardiac adverse events among women treated with trastuzumab for early breast cancer in Lombardy. The cumulative risk of cardiotoxicity was estimated using the Kaplan-Meier method, and independent predictors were assessed using the Cox model.

***Results.*** Of 2,046 trastuzumab users, 53 (2.6%) experienced at least one hospitalization for a cardiac event, and there were two cardiac deaths. The cumulative risk of cardiotoxicity increased up to 2 years after starting treatment, reaching a plateau at 2.8%. The risk was low (0.2%) among young women, whereas the incidence was approximately 10% in women aged ≥70 years, irrespective of cardiovascular risk factors. Age and history of cardiac disease were strong predictors of cardiotoxicity, with a hazard ratio of 11.3 (95% confidence interval [CI]: 3.5–36.6) for women aged ≥70 years as compared with those <50 years of age. Hazard ratio was 4.4 (95% CI: 2.1–9.5) for women with a history of cardiac disease compared with those without a history of cardiac disease.

***Conclusions.*** Cardiotoxicity of trastuzumab varies considerably across subgroups of patients. The long-term safety profile was less favorable than in the largest clinical trial. Strategies to reduce cardiotoxicity in high-risk women should be investigated. ***The Oncologist*** 2013;18:795–801

**Implications for Practice:** Concerns have been raised about the safety profile of trastuzumab for older, less healthy, unselected populations outside of clinical trials. Clinicians need information on the incidence of cardiotoxicity of trastuzumab-based adjuvant regimens in patients with HER-2 positive early invasive breast cancer in clinical practice, according to patient characteristics. This large cohort suggests that the incidence of short-term severe cardiotoxicity (not only congestive heart failure) in clinical practice is higher than that recorded in clinical trials that tested the same regimen. Age and history of cardiac disease are strong predictors of cardiotoxicity. The risk/benefit profile of trastuzumab should be quantitatively assessed, and strategies to reduce cardiotoxicity—especially in older women (≥70 years) and women >50 years of age with several cardiovascular risk factors—should be developed.

## INTRODUCTION

Human epidermal growth factor receptor-2 (HER-2) is a transmembrane tyrosine kinase receptor involved in cell differentiation and proliferation [1]. The HER-2 protein is overexpressed in 20%–25% of breast cancers [2], leading to a poor prognosis and a worse response to treatment, mainly because of an increased growth rate of malignant cells [3, 4].

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Trastuzumab, a recombinant humanized monoclonal antibody, was developed to selectively target the extracellular domain of the HER-2 receptor. Its addition to standard chemotherapy improves disease-free survival (DFS) and overall survival (OS) in HER-2-positive patients [5]. As a result, trastuzumab became standard of care for the treatment of HER-2 metastatic breast cancer and, more recently, for early-stage disease in the adjuvant setting. The Italian Medicine Agency (*Agenzia Italiana del Farmaco* [AIFA]) granted first approval for trastuzumab in early breast cancer treatment when administered after breast surgery, chemotherapy (neoadjuvant or adjuvant), and radiotherapy (if applicable) in 2006 [6].

Although generally well-tolerated, an important issue of concern regarding trastuzumab is cardiotoxicity, especially when combined with certain chemotherapies. A recent meta-analysis of data from clinical trials on the efficacy and safety of trastuzumab included more than 10,000 women with HER-2 early breast cancer and without previous cardiovascular diseases. The relative risk of congestive heart failure (CHF) among patients who received the drug for more than 6 months was 5.11 (90% confidence interval [CI]: 3.00–8.72) [7].

The incidence of trastuzumab-related cardiac events in older, less healthy, unselected populations in routine clinical practice may differ from that in clinical trial settings [8–12]. Consequently, information on the incidence of cardiotoxicity of trastuzumab in clinical practice according to patient characteristics is needed to define the risk/benefit profile.

Using regional health care administrative databases, we assessed trastuzumab-related cardiotoxicity (serious enough to warrant hospitalization) in a large cohort of Italian women with early invasive breast cancer treated between 2006 and 2009. In particular, our objectives were to (a) evaluate the frequency of trastuzumab-related serious cardiac events in clinical practice, (b) assess the cumulative incidence of cardiac disorders at 1, 2, and 3 years after first administration, irrespective of drug discontinuation, and (c) identify predictors for the onset of cardiotoxicity.

## Patients and Methods

The study included women living in Lombardy (an Italian region with 9.5 million inhabitants) who received trastuzumab for early breast cancer between 2006 and 2009, using four regional health administrative databases [13]. The first source of data was the File F registry for 2004–2010. The File F was primarily instituted for reimbursements among different Italian regions and different local health authorities within the same region. It includes all prescriptions of drugs administered directly in the outpatient setting and of selected novel high-cost drugs administered both in the outpatient setting and in the day hospital (DH) in Lombardy and reimbursed by the National Health Service (NHS) [14]. It lists the AIFA input on the market authorization code (*Autorizzazione all'Immissione in Commercio* [AIC]) of the drug package, the unique identification code of the patient receiving the drug, the date and dosage, and also the hospital and physician administering the drug.

The second source of data was the regional hospital discharge forms (*Scheda di Dimissione Ospedaliera* [SDO]) database (2001–2010), which stores hospital discharge records from any Lombardy hospital. These are an integral part of the medical record and report detailed information about patients and their hospitalizations (both ordinary and in the DH), including the unique identification code, demographic characteristics, admission and discharge dates, the main diagnosis and five secondary diagnoses (coded according to the *International Classification of Disease, Ninth Revision* [ICD-9]), date and type of up to five interventions, and hospitalization-related costs (coded according to the national diagnosis-related group system [DRG]) [15]. Since 2006, the SDOs referring to chemotherapy also included information on whether the cost of the drug was compensated through the File F scheme.

The third source of data was the Registry Office database of Lombardy, updated April 2011, which includes information on vital statistics and (if applicable) date of death of Lombardy residents. The fourth source of data was the regional outpatient drug prescription database (2000–2009), which stores all drug prescriptions reimbursed by the NHS and dispensed by a pharmacy in Lombardy. In all databases, the patient was identified by the same unique anonymous code, created through a one-to-one correspondence with the fiscal code by *Regione Lombardia* for each Lombardy resident, to retrieve information while protecting patient's privacy.

### Study Population and Data Analysis

To identify trastuzumab users for early breast cancer treatment, we carried out a computerized record linkage between the File F and the SDO database through the unique anonymous patient identification code. Trastuzumab users were defined as patients having at least one File F record between August 2006 and December 2009 with the drug code 034949014, which corresponds to trasuzumab according to the AIFA AIC. For these subjects, we looked in the SDO database for any record reporting a breast cancer diagnosis (ICD-9 174, 175, V103) prior or concurrent with the first trastuzumab prescription. To restrict the cohort to trastuzumab users for early breast cancer in adjuvant setting, we excluded all patients with SDOs reporting distant recurrence (ICD-9 196.0–196.2, 196.5–196.6, 196.8–196.9, 197.0–197.8, 198.0–198.7, 198.81–198.82, 198.89, 199.0) prior or within 90 days from the first trastuzumab prescription. We also used the File F registry 2010 to retrieve trastuzumab prescriptions of the selected sample.

Information about breast cancer-related health interventions was extracted from the SDO database identifying codes related to breast surgery and neoadjvant/adjuvant chemotherapies in the period between the first breast cancer diagnosis and the first trastuzumab prescription. For chemotherapy, we also searched in the File F registry for any prescription of the oncologic drugs usually employed in early breast cancer treatment in the same period.

To evaluate cardiovascular risk factors prior to trastuzumab administration, including dyslipidemia, diabetes, hypertension, obesity, and history of cardiac disease, we retrieved SDOs reporting these conditions before the first trastuzumab administration. We looked for prescriptions of drugs related to these diseases in the outpatient drug prescription database in the same period, using previously developed algorithms [16–18].

To assess the frequency of cardiac adverse events, we looked for SDOs reporting any ICD-9 code referring to possibly drug-induced cardiac diseases in the main diagnosis for which the date of admission was after the first trastuzumab adminis-

tration. The included diseases were myocardial infarction/ischemia (CD-9 410–411, 413–414), heart failure (CD-9 428, 429, 429.1, 429.3, 785.51), rhythm disorders (CD-9 426–427, 785.0–785.1), and cardiac dysfunctions (CD-9 402.11, 402.91, 425, 425.8, 425.9, 794.30, 997.1). We excluded SDOs with a main diagnosis of congenital conditions, rheumatic disease, endocarditis, and pure valvulopathies. If an SDO also reported death during hospitalization and no other severe condition apart from the cardiac one, we considered it to be a cardiac death.

The combination with paclitaxel was defined as the presence of a prescription of paclitaxel in the File F registry within 2 days from each trastuzumab prescription, on the basis of the approved regimen reported on the drug information technical dossier.

The overall cumulative risk of cardiovascular adverse events and the cumulative risk stratified for age (<70, ≥70 years) was estimated using the Kaplan-Meier method. Each member of the cohort accumulated person-years of follow-up from the first trastuzumab prescription date until the earliest among the following: date of first hospital admission for cardiac diseases (myocardial infarction/ischemia, heart failure rhythm disorders, cardiac dysfunctions) as recorded in the SDO database, death, emigration, or December 31, 2010.

The effect of potential predictors on the risk of cardiac diseases was estimated by a Cox proportional hazards model and expressed as a hazard ratio (HR) and its 95% CI. The model included the following variables: age (<50, 50–59, 60–69, and ≥70 years), previous history of cardiac diseases, selected cardiovascular risk factors (obesity, hypertension, diabetes, and dyslipidemia) before the first prescription of trastuzumab, and combination therapy with paclitaxel.

## Results

In all, 2,879 Lombardy residents had at least one trastuzumab prescription during the study period, for a total of 39,595 trastuzumab prescriptions. We excluded 56 patients without any SDO reporting breast cancer, 41 patients with SDOs reporting breast cancer only after the first trastuzumab prescription, and 25 patients with inconsistent dates. Of the remaining 2,757 patients, 707 were excluded because a diagnosis of metastasis was reported before or within 90 days after the first trastuzumab administration. Four patients were excluded because they were men. Therefore, a total of 2,046 women who received the drug in early breast cancer adjuvant setting were included. The main baseline clinical characteristics are given in Table 1. Approximately two thirds of patients were younger than 60 years. Node-positive status was reported for 43.6% of cases. Conservative breast surgery (57.3%) was more frequent than radical procedures (32.2%). Any previous chemotherapy was administered mainly in the adjuvant setting (87%). In all, 52 (2.5%) patients had history of cardiac disease.

The median number of trastuzumab prescriptions was 17. The median duration of therapy was 11.9 months and the median frequency of administration was 21 days. There were no significant differences in the median number of prescriptions by baseline characteristics of trastuzumab users. Eight percent of patients received trastuzumab in combination with paclitaxel; the remaining 92% of patients received trastuzumab alone.

**Table 1.** Baseline characteristics of 2,046 women administered trastuzumab for early stage invasive breast cancer between 2006 and 2009 in Lombardy, Italy

| Characteristic | *n* (%) |
|---|---|
| Overall | 2,046 |
| Age[a] | |
| <50 yr | 794 (38.8) |
| 50–59 yr | 585 (28.6) |
| 60–69 yr | 493 (24.1) |
| ≥70 yr | 174 (8.5) |
| Nodal status | |
| Positive | 892 (43.6) |
| Negative | 1,154 (56.4) |
| Year of first administration | |
| 2006 | 203 (9.9) |
| 2007 | 403 (19.7) |
| 2008 | 746 (36.5) |
| 2009 | 694 (33.9) |
| Surgery[b] | |
| Conservative | 1,173 (57.3) |
| Radical | 659 (32.2) |
| Unknown | 214 (10.5) |
| Chemotherapy | |
| Yes | 1,845 (90.2) |
| Adjuvant | 1,605 |
| Neoadjuvant | 149 |
| Undefined | 91 |
| No | 201 (9.8) |
| Previous history of cardiac diseases | |
| Yes | 52 (2.5) |
| Myocardial infarction/ischemia | 13 (0.6) |
| Heart failure | 9 (0.4) |
| Rhythm disorders | 36 (1.8) |
| Cardiac dysfunctions | 3 (0.1) |
| No | 1994 (97.5) |

[a]Age at first breast cancer diagnosis reported in regional hospital discharge form database.
[b]For 59 patients, surgery was reported after the beginning of trastuzumab treatment.

Table 2 gives the occurrence of trastuzumab-related cardiac adverse events and distribution by age, combination with paclitaxel, and previous cardiovascular risk factors. Overall, 53 patients (2.6%) experienced at least one cardiac adverse event requiring hospitalization, and there were two cardiac deaths. Twenty-eight women (1.4%) developed CHF, 12 (0.6%) had myocardial infarction/ischemia, 21 (1%) developed rhythm disorders, and 9 (0.4%) had unspecified cardiac dysfunctions. The percentage of women experiencing cardiovascular events increased with age; this percentage also was higher for women with previous cardiovascular risk factors and when trastuzumab was administered with paclitaxel.

Figure 1 shows the cumulative risk of cardiotoxicity, overall and by age. Risk increased up to the second year after the

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**Table 2.** Cardiac adverse events among 2,046 women administered trastuzumab for early stage invasive breast cancer between 2006 and 2009 in Lombardy, Italy

| Event | Yes (%) | No (%) |
|---|---|---|
| At least one event | 53 (2.6) | 1,993 (97.4) |
| Cardiac death | 2 (0.1) | |
| Myocardial infarction/ischemia | 12 (0.6) | |
| Heart failure | 28 (1.4) | |
| Rhythm disorders | 21 (1.0) | |
| Cardiac dysfunctions | 9 (0.4) | |
| Age[a] | | |
| <50 yr | 4 (0.5) | 790 (99.5) |
| 50–59 yr | 15 (2.6) | 570 (97.4) |
| 60–69 yr | 18 (3.7) | 475 (96.3) |
| ≥70 yr | 16 (9.2) | 158 (90.8) |
| Combination with paclitaxel | | |
| Yes | 8 (4.8) | 160 (95.2) |
| No | 45 (2.4) | 1,833 (97.6) |
| Previous cardiovascular risk factor[b] | | |
| At least one risk factor | 40 (4.0) | 949 (96.0) |
| Diabetes | 9 (7.3) | 114 (92.7) |
| Hypertension | 39 (4.4) | 852 (95.6) |
| Dyslipidemia | 14 (4.9) | 271 (95.1) |
| Obesity | 3 (15.0) | 17 (85.0) |
| History of cardiac diseases[c] | 9 (17.3) | 43 (82.7) |
| No risk factor | 13 (1.2) | 1,044 (98.8) |

[a]Age at breast cancer diagnosis.
[b]Any risk factor before the beginning of trastuzumab treatment.
[c]Any cardiac event before the beginning of trastuzumab treatment.

beginning of treatment, reaching a plateau at 2.8% from the third year onwards. The cumulative risk for subjects <70 years of age and for those ≥70 years were respectively 1.34% and 6.43% after 1 year, 1.96% and 9.83% after 2 years, and 2.19% and 9.83% after 3 years.

Table 3 shows the combined distribution of cardiac adverse events by age and previous cardiovascular risk factors. There was only one episode of cardiotoxicity in women <50 years of age who had no cardiovascular risk factors (0.2%). Cardiotoxicity increased with age in women with or without risk factors. At younger ages, cardiac adverse events were more frequent among women with previous risk factors.

Table 4 shows the HR of cardiac adverse events estimated from a proportional hazard model. HR increased with age and was 11.3 (95% CI: 3.5–36.6) in patients ≥70 years of age, as compared to those <50 years of age. The HR was 4.4 (95% CI: 2.1–9.5) in women with a previous history of cardiac disease, 1.7 (95% CI: 0.9–3.4) among women with other selected cardiovascular risk factors, and 2.2 (95% CI: 1.0–4.7) among those treated in combination with paclitaxel.

## Discussion

The present study provides extensive data on the cardiac safety profile of trastuzumab for early breast cancer in the adjuvant setting from the largest data set to date (>2,000 women). Overall, the percentage of women who experienced at least one symptomatic cardiac adverse event that was serious enough to require hospitalization was 2.6%. CHF was the most common cardiac disease recorded (1.4%), whereas rhythm disorders and myocardial infarction/ischemia occurred in 1% and 0.6% of trastuzumab users, respectively. There were two cardiac deaths (0.1%).

It is difficult to directly compare our results with those from clinical trials because of the different definitions of cardiac disease, the differences in the baseline characteristics of the populations, and the lack of a control group. Data on asymptomatic decline in left ventricular ejection fraction or symptomatic CHF not requiring hospitalization were not available in our study because the SDO database does not include details about physical examinations, symptoms, serological tests (i.e., brain natriuretic peptide), or echocardiography results.

Previous experimental [7] and observational investigations [8, 9, 19, 20] generally recorded rates of asymptomatic and symptomatic CHF, although using different clinical and echocardiographical parameters to define it. However, in the current study, we considered only cardiac diseases leading to hospital admission, which therefore were of a high degree of severity. Our patients with "hospitalized" CHF may be roughly compared with patients with severe CHF (identified as New York Heart Association class III/IV [21]), in the Herceptin Adjuvant (HERA) trial, the largest study leading to approval of the regimen administered in the majority of our patients (i.e., trastuzumab given alone every 3 weeks up to 1 year or to disease progression after adjuvant chemotherapy) [22]. If anything, our data may underestimate severe CHF. However, we found an approximately threefold higher cumulative incidence (1.4%) than that recorded in the HERA trial, which reported an incidence rate of 0.54%. This may partly be due to the fact that the HERA trial population was younger (i.e., median age of 52 years) with no cardiovascular risk factors. In fact, in our study, the increase in the risk of possibly trastuzumab-related adverse events was larger in older women and those with cardiovascular risk factors.

Given the lack of a comparison group, the issue of whether these events are in fact due to trastuzumab treatment or simply to the different baseline characteristics of the population remains open to discussion. The cumulative risk increased in the first 2 years after starting trastuzumab and leveled off in the third year after stopping treatment. This suggests that most of the events observed during or soon after treatment might indeed be attributable to the drug.

Trastuzumab-related cardiotoxicity has been reported to be transient and largely reversible after stopping treatment [22]. In our study, however, the cumulative incidence risk increased even in the second year after starting treatment, whereas no further increase was seen in the third year. Approximately half (51%) of the cardiac events occurred during treatment (within the first month after the last trastuzumab administration). Six cardiac events (11%) occurred during the second and third month after the end of treatment, likely reflecting the low systemic clearance of the drug (half-life: 28.5 days), whereas the remaining 20 events (38%) occurred from the fourth month onward.

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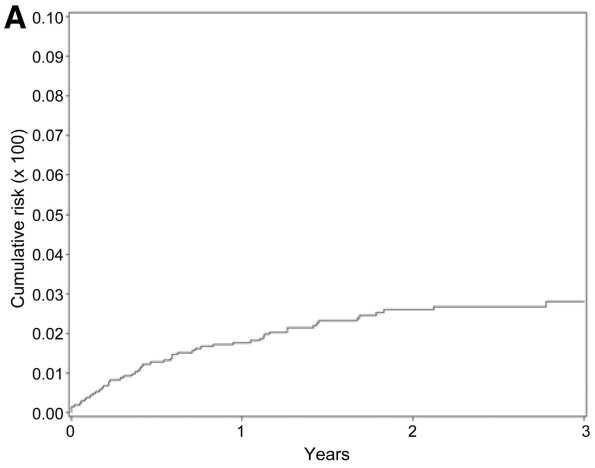
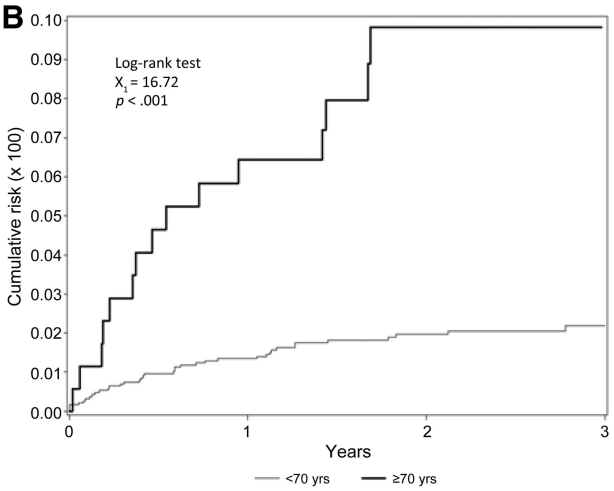



| | Years from beginning of treatment | | |
|---|---|---|---|
| | 1 year | 2 year | 3 year |
| Cumulative risk | 1.77 | 2.58 | 2.79 |
| Events | 36 | 14 | 2 |
| Number at risk | 1964 | 1239 | 522 |




| | Years from beginning of trastuzumab | | |
|---|---|---|---|
| | 1 year | 2 year | 3 year |
| <70 yrs | | | |
| Cumulative risk | 1.34 | 1.96 | 2.19 |
| Events | 25 | 10 | 2 |
| Number at risk | 1810 | 1164 | 505 |
| ≥70 yrs | | | |
| Cumulative risk | 6.43 | 9.83 | 9.83 |
| Events | 11 | 4 | 0 |
| Number at risk | 154 | 75 | 17 |

**Figure 1.** Cumulative risk of cardiotoxicity among 2,046 trastuzumab users for early stage invasive breast cancer overall **(A)** and by age **(B)**.

**Table 3.** Cardiac adverse events according to age and selected previous cardiovascular risk factors among 2,046 women administered trastuzumab for early stage invasive breast cancer between 2006 and 2009 in Lombardy, Italy

| | At least one cardiovascular risk factor ($n$ = 989) | | No cardiovascular risk factors ($n$ = 1,057) | |
|---|---|---|---|---|
| Age[b] | Total (%) | Cardiac adverse events[a] (%) | Total (%) | Cardiac adverse events[a] (%) |
| <50 yr | 214 | 3 (1.4) | 580 | 1 (0.2) |
| 50–59 yr | 266 | 10 (3.8) | 319 | 5 (1.6) |
| 60–69 yr | 363 | 14 (3.9) | 130 | 4 (3.1) |
| ≥70 yr | 146 | 13 (8.9) | 28 | 3 (10.7) |

[a]Cardiac adverse events include any cardiac event after the beginning of trastuzumab treatment.
[b]Age is at breast cancer diagnosis.

With reference to combination therapy, anthracycline-based regimens induce a dose-dependent and irreversible cardiotoxicity. This effect can be further enhanced by the administration of trastuzumab, especially when the two drugs are administered simultaneously, which blocks the HER-2 signaling necessary for the growth, protection, and repair of cardiomyocytes, as well as for the modulation of anthracycline-related myofibrillar injuries [23, 24]. It is therefore important to determine simultaneous or sequential use of the two drugs. However, we had incomplete information on drugs administered in the neoadjuvant/adjuvant chemotherapy context because the File F registry mandatorily included only the codes of

**Table 4.** Hazard ratios and corresponding 95% confidence intervals for cardiac events versus no cardiac events among 2,046 women administered trastuzumab for early stage invasive breast cancer between 2006 and 2009 in Lombardy, Italy

| Characteristic | $n$ | % | HR[a] (95% CI) |
|---|---|---|---|
| Age | | | |
| <50 yr | 794 | 38.8 | 1[b] |
| 50–59 yr | 585 | 28.6 | 4.6 (1.5–13.9) |
| 60–69 yr | 493 | 24.1 | 5.4 (1.7–16.6) |
| ≥70 yr | 174 | 8.5 | 11.3 (3.5–36.6) |
| Previous selected cardiovascular risk factors[c] | | | |
| No | 1,065 | 52.0 | 1[b] |
| Yes | 981 | 48.0 | 1.7 (0.9–3.4) |
| History of cardiac diseases | | | |
| No | 1,994 | 97.5 | 1[b] |
| Yes | 52 | 2.5 | 4.4 (2.1–9.5) |
| Association with paclitaxel | | | |
| No | 1878 | 91.8 | 1[b] |
| Yes | 168 | 8.2 | 2.2 (1.0–4.7) |

Hazard ratios and 95% confidence intervals are shown.
[a]Estimated by Cox model including terms for age, previous risk factor, previous cardiac event, and association with paclitaxel.
[b]Reference category.
[c]Includes obesity, hypertension, diabetes, and dyslipidemia.
Abbreviations: CI, confidence interval; HR, hazard ratio.

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high-cost new drugs (including paclitaxel and docetaxel). In particular, we were unable to identify patients using anthracycline-based therapy. However, AIFA does not allow the simultaneous administration of trastuzumab and anthracyclines. At the time of the study, AIFA granted approval for trastuzumab either alone every 3 weeks or combined with paclitaxel every week, but only "after surgery (neoadjuvant/adjuvant) chemotherapy and radiotherapy (if applicable)." Therefore, anthracycline treatment, if administered, could have only been sequential. Furthermore, according to the Italian Association of Medical Oncology guidelines for Lombardy [25], adjuvant regimens for high-risk breast cancer (which includes HER-2-positive cancers) must include anthracyclines and/or taxanes. We found 347 patients who received a taxane-based regimen in the neoadjuvant/adjuvant setting, for whom we did not know if they also received anthracyclines. For the remaining patients, however, it is very likely that at least an anthracycline-based regimen was administered in the adjuvant context. Therefore, we can assume that the majority of our patients received an anthracycline-based regimen prior to trastuzumab administration but virtually none received it simultaneously.

The long-term cardiac safety profile in our data set is less favorable than that reported in the HERA study (0.8% at 3.6 years), [26], although it is in line with the results of Perez et al. [27], who reported a cumulative incidence of cardiotoxicity of 2.8% at 2 years and 3.3% at 3 years among women treated with doxorubicin and cyclophosphamide followed by trastuzumab-containing therapy— higher than that recorded in the arm with no sequential addiction of trastuzumab (0.2% at 2 years and 0.3% at 3 years).

Potential predictors of trastuzumab-related cardiotoxicity were investigated in several studies [8, 9, 19, 20]. These predictors include traditional cardiovascular risk factors, such as older age, obesity, smoking, dyslipidemia, hypertension, diabetes, history of cardiac disease, and selected clinical and serological parameters, such as renal function blood test and hemoglobin. In our study, age was a strong predictor of cardiotoxicity; the HR was 10-fold higher in women aged $\geq$70 years as compared with women younger than age 50. In all, 9% of women older than 70 years were hospitalized for a cardiac event after trastuzumab treatment. Although the number of women older than 70 years was limited, our results suggest that the use of trastuzumab in older women must be considered with care. Only 53 women with documented history of cardiac events were included in this cohort; 9 of these women (17%) experienced another event after trastuzumab treatment, corresponding to a HR of 4. With regard to the presence of cardiovascular risk factors in the absence of overt disease, we found a 70% increased HR after adjustment for age and other covariates; however, this was not significant. Hypertension, diabetes, and dyslipidemia among our patients were collected from SDO diagnosis fields and/or outpatient drug prescriptions database; therefore, such conditions were likely to be somewhat underestimated. However, the women involved in this study had repeated contact with health care providers, including hospitalizations, because of their breast cancer. It is therefore unlikely that some conditions, such as diabetes and hypertension, were not identified and treated—at least in severe cases. On the other hand, women with a higher cardiovascular risk were probably excluded from trastuzumab treatment.

A major limitation of the use of health care databases for epidemiologic and clinical research is the lack of information on selected potential covariates. For example, we had no data on smoking habits and familial history of heart disease. The administrative purpose for which these data sets were primarily instituted may also limit the completeness and accuracy of the medical information reported [13, 28]. The main advantage of these data sets is the representativeness of routine clinical practice because they refer to all medical interventions reimbursed by the NHS, which covers all residents. Other strengths include the large number of observations, the length of follow-up, and the inclusion of all age groups. Moreover, the concordance of most data between and within the four databases used in this study is reassuring in terms of reliability and validity of available information.

## Conclusion

Our data suggest that the incidence of short-term severe cardiotoxicity (not only CHF) in clinical practice is higher than that recorded in a clinical trial testing the same regimen [22]. In addition, the incidence varies substantially across subgroups of patients. The risk-benefit profile of trastuzumab should be assessed in older women (>70 years), as well as women >50 years of age with cardiovascular risk factors. For these women, the investigation of clinical strategies to prevent cardiotoxicity is warranted [29].

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